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# Pulmonary function in patients with pandemic H1N1

## *Prova de função pulmonar em pacientes com H1N1pandêmica*

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**Introduction:** The influenza A (H1N1) was responsible for the 2009 pandemic, especially with severe pulmonary complications. **Objective**: To describe characteristics of patients in a university hospital in Curitiba - PR with laboratory diagnosis of influenza A (H1N1) and its post hospital discharge in the 2009 lung function pandemic **Methodology**: A retrospective observational study. It was used as a data source the institution Epidemiology Service (SEPIH) and spirometry tests of patients who were admitted in 2009, 18 years without lung disease associated and non-pregnant. Descriptive statistics were used and applied Fisher's exact test for relationship between comorbidity and spirometry tests. **Results**: There were 84 confirmed cases, of these 11 were eligible for the study with a mean age of 44.27 years (± 9.63) and 63.63% males. 54.54% of the 11 patients had comorbidities associated with systemic arterial hypertension (54.54%), diabetes (18.18%) and late postoperative period of kidney transplantation (18.18%) were the most frequent. Most patients (81.81%) had BMI ≥ 25kg / $m^2$. The Spirometry test was performed approximately 40.09 (± 15.27) days after discharge, of these, 5 had restrictive pattern and all had abnormal chest radiograph results. There was no statistically significant difference between the results of Spirometry and comorbidities (p=0.24). **Conclusions**: The group evaluated in this research did not show a direct relationship between Spirometry and comorbidities, but changes in Spirometry in some patients after hospital discharge stood out, suggesting changes in lung function due to influenza A (H1N1).

**Keywords**: Influenza A Virus. Respiratory Function Tests. Pandemics.

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***Resumo***

***Introdução:*** *O vírus influenza A (H1N1) foi responsável pela pandemia de 2009, com graves complicações principalmente pulmonares.* ***Objetivo****: descrever características dos pacientes de um hospital universitário da cidade de Curitiba – PR com diagnóstico laboratorial de influenza A (H1N1) e a sua função pulmonar pós alta hospitalar na pandemia de 2009.* ***Metodologia****: estudo retrospectivo observacional. Utilizou-se como fonte de dados o Serviço de Epidemiologia da instituição (SEPIH) e exames de espirometria de pacientes que estiveram internados em 2009, maiores de 18 anos, sem doença pulmonar associada e não gestantes. Foi utilizado estatística descritiva e aplicado o teste exato de Fisher para relação entre comorbidades e exames de espirometria.* ***Resultados****: 84 casos confirmados, destes 11 foram elegíveis para o estudo com média de idade de 44,27 anos (±9,63), sendo 63,63% do gênero masculino. Dos 11 pacientes 54,54% possuíam comorbidades associadas sendo a hipertensão arterial sistêmica (54,54%), diabetes (18,18%) e pós operatório tardio de transplante renal (18,18%) as mais frequentes. A maioria dos pacientes (81,81%) apresentaram o IMC ≥25kg/m$^2$. O exame de espirometria foi realizado cerca de 40,09 (±15,27) dias após a alta, destes, 5 apresentaram padrão restritivo e todos apresentaram alterações na radiografia do tórax. Não houve diferença estatisticamente significativa entre os resultados apresentados pela espirometria e a relação com comorbidades (p=0,24).* ***Conclusão****: o grupo avaliado por esta pesquisa não apresentou relações diretas entre a espirometria e comorbidades associadas, porém destacou-se alterações na espirometria em alguns dos pacientes pós alta hospitalar, sugerindo alterações da função pulmonar em decorrência da influenza A (H1N1).*

***Palavras-chave****: Vírus da Influenza A. Testes de Função Pulmonar. Pandemias.*

## Introduction

In the end of the 80's there was an outbreak of infection by the Influenza A virus (H1N1) in a region of the United States of America (USA) especially attacking young people with a significant morbidity (1), bringing about a subsequent mass vaccination. A few decades later this virus re-appeared in an overpowering manner in mid 2009. The first cases were detected precisely on April 11$^{th}$ 2009 in the city of Veracruz in Mexico, and it went on to becoming a level 6 pandemic in the beginning of June of the same year, thus defining the gravity of the pathology caused by the virus and its geographical extension (2, 3).

According to the World Health Organization (WHO) (3), from April to December 2009, 208 countries were notified, in total 12,799 deaths from Influenza A (H1N1) confirmed by laboratory exams. Brazil registered a total of 2,051 deaths. The southern region presented a higher rate of mortality, being 3/100 thousand inhabitants (840 deaths) (4, 3).

The symptoms of Influenza A (H1N1), similar to the common cold, were stronger and harder to control. Many of the affected individuals evolved to death in a matter of hours, even with the best support of an Intensive Care Unit (ICU) (5). In the more serious cases, survivors presented great bilateral pulmonary damage in 2 or more quadrants and signs of aveolar infiltrates with a substantial systemic inflammatory response, evidenced by radiography. These alterations had a great impact on oxygenation and induced severe pulmonary lesion (2, 6, 7, 8).

The research of Marchiori et al. (9) and Nin et al. (10) showed pulmonary histopathology in patients contaminated with H1N1 after death. In general they presented diffuse alveolar exudative damage, varying degrees of hemorrhage and alveolar edema, necrosis and sloughing of the epithelium of the bronchioles, atelectasis of the alveoli and records of thrombus.

In the midst of this new information regarding the behavior of Influenza A (H1N1), uncertainties about the possible harm appeared, especially in the respiratory system. In the research conducted by Tougen Junior et al. (11) patients were evaluated two and six months after ICU discharge, the pulmonary function exams showed reduced forced vital capacity (FVC) and a low carbon monoxide diffusion capacity. In another research which evaluated lung function and quality of life, no changes were perceived 6 months after hospital discharge (12). One of the most widely used exams to evaluate lung function is Spirometry, which permits the diagnosis and quantification of respiratory disorders, which can be restrictive, obstructive or mixed. This exam can aid in the prevention and also in registering the evolution of a disease and and its severity (13).

A recent study showed that the pandemic of influenza A (H1N1) presented different characteristics from the seasonal influenza (14). Seeking to better comprehend the process of this pathology, the aim of this study was to describe the characteristics of patients in a university hospital in the city of Curitiba – PR with the laboratory diagnosis of influenza A (H1N1) and their lung capacity after hospital discharge in the 2009 pandemic.

## Methods

This retrospective observational study was conducted in the Hospital de Clinicas of Univesidade Federal do Paraná, with the approval of the Ethics in Research Committee HC-UFPR (CAAE: 12420313.2.0000.0096). As a database, the Epidemiology Service of the same institution was used (SEPIH). Data was collected only from hospital records referent to the period of April to December 2009 obtaining a total of 84 confirmed cases of influenza A (H1N1). This information was gathered by only one researcher, protecting all the ethical principles set by the 196/96 resolution. The data collected was identification information, anthropometric measurements, associated lung diseases, comorbidities, smoking history, length of hospital stay, use of invasive or noninvasive mechanical ventilation, extra supply of oxygen, x-ray pattern according to the notification form of the Notifiable Diseases Information System (SINAN), use of Oseltamivir, and results of Spirometry exams for volume of forced exhaled air in the first second (FEV1), forced vital capacity (FVC); ratio of forced exhaled volume in the first second and forced vital capacity (FEV1/FVC); total lung capacity (TLC) and functional residual capacity (FRC). The patients included in the study were hospitalized in the HC – UFPR hospital during the referred period with a laboratory diagnosis of influenza A (H1N1), who did not die during hospitalization, with age above 18 years, without associated lung disease, non-pregnant and who underwent the Spirometry exam in 2009. All the data was compiled in a Microsoft Excel (2010) database and descriptive statistics were applied with the use of mean and standard deviation. For the statistical analysis BioSat 5.0 software was used and Fisher's Exact Test was applied for comorbidities and Spirometry exams. The statistical significance level adopted was $p < 0.05$.

## Results

In the 2009 Influenza A (H1N1) pandemic, 84 cases were confirmed in the HC-UFPR. Among these 40.47% were male and 59.52% were female. After applying the established inclusion criteria, 73 of the initial 84 patients were excluded from the research; due to death (28 patients), pregnancy (7 patients), being under 18 years old (24 patients), presenting associated lung disease (6 patients) or not undergoing the Spirometry exam (8 patients), leaving a total of 11 apt patients.

Out of the 11 patients who underwent the lung function exam, the mean age was 44.27 years (± 9.63), being 63.63% of male gender and 36.36% female. The comorbidities found were hypertension (54.54%), diabetes (18.18%), kidney transplantation (18.18%), acute myocardial infarction (9.09%), dyslipidemia (9.09%), systemic lupus erythematosus (9.09%), hypothyroidism (9.09%), depression (9.09%) and alcoholism (9.09%). The remaining individuals (45.45%) did not present comorbidities (Table 1). The body mass index (BMI) was classified separately, according to the World Health Organization (15), the patients were classified as ideal weight (18.18%), overweight (36.36%), grade I obesity (9.09%), grade II obesity (27.27%) and morbid obesity (9.09%).

Regarding smoking, 27.27% were smokers with an average smoking history of 21.66 years/pack (± 7.63). The average time of hospitalization was 12.27 days (± 9.05). As for the location, 3 patients were in the Intensive Care Unit for approximately 7.33 days (± 7.09), one being in invasive mechanical ventilation for 12 days and two in noninvasive mechanical ventilation for on average 2,5 days, the other patients demanded extra oxygen supply of low or high flow and were hospitalized in the infirmaries (6) and in the Semi-Intensive Care unit (2). The x-ray pattern according to SINAN was classified presenting interstitial infiltrate (36.36%); consolidation (36.36%) and the remaining patients (27.27%) a mixed pattern (Table 1). All used the medication Oseltamivir during hospitalization.

The Spirometry exam executed by the Lung Function Service of HC was done approximately 40.09 (± 15.27) days after discharge. Among these, 5 presented a restrictive pattern, being that 4 were evaluated with low degree and 1 with moderate degree (Table 1). There was no statistically significant difference between the results of the Spirometry exam and comorbidities ($p = 0.24$). Even though 4 out of 5 cases that presented alterations in the Spirometry also presented associated comorbidities.

**Table 1** - Post hospital discharge Spirometry with an average of 40.09 (±15.27) days and associated characteristics

| Patients | FVC (% predicted) | VEF1 (% predicted) | VEF1/FVC (% predicted) | TLC (% predicted) | FRC (% predicted) | Spirometry | Comorbidities N | BMI (kg/m²) | X-Ray pattern according SINAN |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.18 (69) | 2.64 (72) | 83 (102) | 4.9 (72) | 2.61 (76) | RLD low | 2 | morbid obesity | consolidation |
| 2 | 2.19 (56) | 1.83 (58) | 84 (101) | 3.64 (62) | 2.47 (87) | RLD moderate | 0 | overweight | consolidation |
| 3 | 3.36 (80) | 2.92 (87) | 87 (105) | 4.77 (78) | 2.26 (76) | RLD low | 2 | obesity GI | Interstitial infiltrate |
| 4 | 2.68 (78) | 2.25 (79) | 84 (97) | 5.31 (112) | 3.16 (124) | RLD low | 5 | overweight | consolidation |
| 5 | 1.96 (71) | 1.82 (80) | 93 (110) | 3.77 (84) | 1.78 (72) | RLD low | 2 | obesity GII | mixed |
| 6 | 3.94 (110) | 3.41 (115) | 86 (101) | 7.46 (146) | 4.1 (146) | normal | 0 | obesity GII | interstitial infiltrate |
| 7 | 3.72 (108) | 3.15 (116) | 85 (104) | 5.12 (89) | 3.15 (110) | normal | 0 | ideal weight | consolidation |
| 8 | 4.54 (103) | 3.84 (109) | 85 (101) | * | * | normal | 0 | ideal weight | mixed |
| 9 | 4.12 (129) | 2.63 (104) | 64 (78) | 6 (119) | 2.91 (115) | normal | 3 | overweight | interstitial infiltrate |
| 10 | 2.97 (95) | 2.42 (94) | 82 (95) | 4.85 (105) | 2.27 (90) | normal | 4 | obesity GII | mixed |
| 11 | 3.96 (103) | 3.13 (104) | 79 (97) | 6.5 (105) | 3.4 (108) | normal | 0 | overweight | interstitial infiltrate |

Note: FCV = forced vital capacity; FEV1 = volume of forced exhaled air in the first second; FEV1/FVC ratio of forced exhaled volume in the first second and forced vital capacity; TLC = total lung capacity; FRC = functional residual capacity; BMI = body mass index; SINAN = Notifiable Diseases Information System; RLD = restrictive lung disease; Obesity: GI = grade one; GII = grade two.

## Discussion

The 2009 Influenza A (H1N1) pandemic impelled the worldwide population, there was a broad description of signs and symptoms of a pathology unknown at the time, and its management became important for subsequent actions (7). All around the world the confirmed cases and registers of Influenza A (H1N1) permitted detailed analyses of the evolution of this pandemic, seeking its prevention and minimizing the risk (16).

The confirmed cases in HC-UFPR during the period of April to December 2009 are similar to some other findings in specialized literature, however they do not characterize a pattern. Of the 11 patients included in this study all were young adults and most of the male gender.

Quispe-Laime et al. (12) presents a study with 11 subjects 6 months following hospital discharge for Influenza A (H1N1), the age group was similar, 37±9 years old, and most were also males (73%). In other publications the average age was of 423 years with a variation between 16 and 92 years, being that most, 53.53%, were females (17) and another in which the average age was 24.9 years, being 64.7% females (18), both studies regarding data from the second semester of 2009 in Brazilian cities.

In and international study with 27 patients, 55.55% presented comorbidities, being the most frequent lung diseases, diabetes and dementia (19). The present study found that 54.54% of the patients had associated comorbidities, the most present being systemic arterial hypertension and diabetes. Zarogoulidis et al. (20) in his study with 44 patients did not find a significant number of associated comorbidities, and when present, the most related were lung diseases, cardiac coronary disease and diabetes.

Lenzi et al. (21) showed that out of 1,827 patients who used Oseltamir on average 2.3 days after the beginning of the symptoms, 11% (201) evolved to death. Based on this data, it was calculated that each passing day to the beginning of the treatment, raises by 40% the chance of death. Furthermore, patients who had associated comorbidities had twice the chance of death than healthy patients (without comorbidities). And each additional comorbidity raised by 60% the chance of death. In this study the most common was diabetes.

Another relevant data refers to the body mass index (BMI), which can be a risk factor for the development of various diseases, and also a significant factor to the worsening of the patient with the Influenza A virus (H1NI) (8). In the present research the data points to a high percentage, 81.81%, of patients with a BMI of ≥25kg/m². Data similar to this was presented by Quispe-Laime et al. (12) in which 73% of the subjects had a BMI of ≥25kg/m², two of which

had a BMI of >40kg/m$^2$. On the other hand, Nicolini et al. (19) found only 2 overweight patients out of the 27 evaluated.

Research shows that among the special groups of population with a risk potential to evolve with serious forms of the disease, are patients with chronic diseases, the morbidly obese and pregnant women (22). Obesity can influence the measure of lung volumes because it interferes in the diaphragmatic movement such as the chest wall, leading to the reduction of the maximum voluntary ventilation (13, 23, 24). The predisposition to infections which obese individuals posses has been described in research, however regarding the respiratory system, precise data has not yet been disclosed, making more research necessary (25).

The habit of smoking was present in 27.27% of the sample, different from the findings of the research of Luyt et al. (26), which analyzed 37 patients, 45.94% of which were smokers. Lenzi et al. (14) related that only 7.1% of the hospitalized patients smoked. These same authors affirmed that smoking was one of the risk factors leading to the hospitalization of the patients along with obesity and other comorbidities. Analyzing the subjects' physical characteristics and comorbidities data, the presented table demonstrates that, in their majority, they fit into a group which is susceptible to hospitalization, on account of most being overweight and presenting some type of comorbidity.

Permanence in hospital raises the risk of complications, studies like those of Nicolini et al. (19) and Luyt et al. (26) present the profile of patients who remained in ICU under mechanical ventilation. Our patients remained on average 12.27 (± 9.05) days hospitalized in different units, only 3 of which in ICU, however all needed extra oxygen supply.

Paredes and Cevallos (2) and Zarogoulidis et al. (20) demonstrated that image exams, such as radiographs, aid in the diagnosis of lung damage. During hospitalization patients with Influenza A (H1N1) presented extensive regions of lung damage, generally with a ground-glass opacity pattern or consolidations. The radiograph was also considered a complication-predictive exam for these patients (27). Which complies with the findings observed in the present research, in which all of the subjects presented this type of damage. Verrastro et al. (28) also found through Computed Tomography exams that the 9 patients in his study presented abnormalities of ground-glass opacity. Furthermore, in 7 of these patients these disturbances were extensive, multiple and bilateral.

For the identification of breathing disorders, presence of the restrictive pattern was verified in 5 out of the 11 evaluated patients, the exam was done around 40 (± 15.27) days after hospital discharge. Similar to our findings, Toufen et al. (11) in his study followed-up 4 patients with Severe Acute Respiratory Syndrome (SARS) at the time of hospitalization for Influenza A (H1N1) who required invasive mechanical ventilation, two months after discharge a lung function exam was completed demonstrating a restrictive pattern in 3 patients and after 6 months the condition remained for 2 patients. Zarogoulidis et al. (20) also discovered abnormal results in lung function immediately after discharge, he verified that FVC and FEV1 were reduced, after 3 months there was improvement which remained similar 6 months after discharge. Liu et al. (29) evaluated 48 patients 1 year after hospital discharge. Finding 22 who had normal lung function despite later relating respiratory infections, however not serious. In addition, 26 showed abnormal results in later lung function exams especially in diffusion.

Quispe-Laime et al. (12) and Edgeworth et al. (30) evaluated patients who had remained in ICU and under mechanical ventilation, 6 months after hospital discharge neither presented abnormal results in Spirometry exams. Luyt et al. (26) evaluated 37 patients with SARS and who remained under mechanical ventilation. In the study, the patients were divided into 2 groups, the first using extra corporeal membrane and the other not. In the evaluation after 1 year neither of the groups presented abnormal results in Spirometry exams, despite not holding statistical significance, when compared, the group which used extra corporeal membrane presented lower numbers than the other group.

## Conclusion

The results suggest that the Influenza A (H1N1) pandemic of 2009 affected especially young adult patients, having or not associated comorbidities, most of them were overweight and all presented abnormal results in radiographic exams. The patients in this study remained hospitalized in different infirmaries and all demanded extra oxygen supply, being only one in invasive mechanical ventilation. The group evaluated through this research did not present direct relations between Spirometry and associated comorbidities,

however abnormal results in Spirometry were discovered after hospital discharge, suggesting lung function damage due to Influenza A (H1N1).

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